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ASPRE trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history

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Condensation

The beneficial effect of aspirin in the prevention of preterm preeclampsia may not apply in pregnancies with chronic hypertension.

Short version of article title

Subgroup analysis of ASPRE trial

ABSTRACT

Objective: To examine whether there are differences in the effect of aspirin on the incidence of preterm-PE in the ASPRE trial in subgroups defined according to maternal characteristics and medical and obstetrical history.

Study design: This was a secondary analysis of data from the ASPRE trial. In ASPRE women with singleton pregnancies had screening by means of an algorithm that combines maternal factors and biomarkers at 11-13 weeks' gestation. Those with an estimated risk for preterm-PE of >1 in 100 were invited to participate in a double-blind trial of aspirin (150 mg/day) vs. placebo from 11 to 14 until 36 weeks' gestation. Aspirin was associated with a significant reduction in the incidence of preterm-PE with delivery at <37 weeks' gestation, which was the primary outcome (odds ratio 0.38; 95% confidence interval, 0.20 to 0.74; P=0.004). Subgroup analysis was performed to assess evidence of differences in the effect of aspirin on incidence of preterm-PE in subgroups defined by maternal age (<30 and ≥30 years), body mass index (<25 and ≥25 kg/m^2), racial origin (Afro-Caribbean, Caucasian and other), method of conception (natural and assisted), cigarette smoking (smoker and non-smoker), family history of PE (present and absent), obstetrical history (nulliparous, multiparous with previous PE and multiparous without previous PE), history of chronic hypertension (present and absent). Interaction tests were performed on the full data set of patients in the intention to treat population and on the data set of patients who took ≥ 90% of the prescribed medication. Results are presented as forest plot with P values for the interaction effects, group sizes, event counts and estimated odds ratios. We

examined whether the test of interaction was significant at the 5% level with a Bonferroni adjustment for multiple comparisons.

Results: There was no evidence of heterogeneity in the aspirin effect in subgroups defined according to maternal characteristics and obstetrical history. In participants with chronic hypertension preterm-PE occurred in 10.2% (5/49) in the aspirin group and in 8.2% (5/61) in the placebo group (adjusted odds ratio 1.29, 95% confidence interval, 0.33 to 5.12); the respective values in those without chronic hypertension were 1.1% (8/749) in the aspirin group and 3.9% (30/761) in the placebo group (adjusted odds ratio 0.27, 95% confidence interval, 0.12 to 0.60). In all participants with adherence of ≥90% the adjusted odds ratio in the aspirin group was 0.24 (95% CI 0.09 to 0.65), in the subgroup with chronic hypertension it was 2.06 (95% CI 0.40 to 10.71) and in those without chronic hypertension it was 0.05 (95% CI 0.01 to 0.41). For the complete data set the test of interaction was not significant at the 5% level (p=0.055), but in those with adherence ≥90%, after adjustment for multiple comparisons, the interaction was significant at the 5% level (p=0.0019).

Conclusions: The beneficial effect of aspirin in the prevention of preterm preeclampsia may not apply in pregnancies with chronic hypertension. There was no evidence of heterogeneity in the aspirin effect in subgroups defined according to maternal characteristics and obstetrical history.

Key words: First trimester screening, Aspirin, ASPRE trial, Preeclampsia, Chronic hypertension, Uterine artery Doppler, Mean arterial blood pressure, Placental growth factor, Pregnancy associated plasma protein-A.

Introduction

This is a secondary analysis of data from the ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial.[1] In the trial, women with singleton pregnancies identified as being at high-risk of preterm preeclampsia (PE), by means of an algorithm that combines maternal factors and biomarkers at 11-13 weeks' gestation,[2] were randomized to receive aspirin (150 mg/day) vs. placebo from 11 to 14 until 36 weeks' gestation. Preterm-PE with delivery at <37 weeks' gestation, which was the primary outcome, occurred in 1.6% (13/798) participants in the aspirin group, as compared with 4.3% (35/822) in the placebo group (odds ratio in the aspirin group with adjustment for the effect of the estimated risk for preterm-PE at screening and participating center 0.38; 95% confidence interval, 0.20 to 0.74; P = 0.004).

The objective of this study is to examine whether there are differences in the effect of aspirin on the incidence of preterm-PE in subgroups defined according to maternal characteristics and medical and obstetrical history.

Methods

The ASPRE trial was conducted at 13 maternity hospitals in the United Kingdom, Spain, Italy, Belgium, Greece, and Israel.[1] In the 13 participating hospitals routine screening for preterm-PE was carried out at 11-13 weeks' gestation by an algorithm combining maternal demographic characteristics and medical and obstetrical history,[3] and the measurements of mean arterial pressure,[4] uterine

artery pulsatility index[5] and serum pregnancy associated plasma protein-A and placental growth factor (PAPP-A and PlGF 1-2-3™ kits, DELFIA® Xpress random access platform; PerkinElmer Inc. Wallac Oy, P.O.Box 10, 20101 Turku, Finland). The eligibility criteria for the trial were maternal age ≥18 years, no serious mental illness or learning difficulties, singleton pregnancy with live fetus with no major abnormality demonstrated on the 11-13 weeks scan and estimated risk for preterm-PE of >1 in 100.[1] Participants completed a questionnaire on their demographic characteristics and medical and obstetrical history and the questionnaire was then reviewed by a doctor together with the woman. Consequently, the diagnosis of chronic hypertension was based on what was reported by the participants at the visit at 11-13 weeks' gestation.

The primary outcome measure was delivery with PE at <37 weeks' gestation. Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy.[6] The systolic blood pressure should be ≥140 mmHg and/or the diastolic blood pressure should be ≥90 mmHg on at least two occasions four hours apart developing after 20 weeks of gestation in previously normotensive women. Hypertension should be accompanied by proteinuria of ≥300 mg in 24 hours or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension.

Adherence was calculated as a percentage of the reported intake of tablets to

the total number that participants were expected to have taken between the date of randomization and the date of the visit at 36 weeks' gestation or the date of delivery if delivery occurred before 36 weeks.

Approval for the trial was obtained from the relevant research ethics committee and competent authority in each country in which the trial was conducted. These include the NHS Health Research Authority in the UK; Ethics Committee of Clinic University Hospital Virgen de la Arrixaca, Murcia, Spain; Ethics Committee of University Hospital of San Cecilio, Granada, Spain; Comite de etica e investigacion, Hospital Universitario Nuestra Senora de la Candelaria, Tenerife, Canary Islands; Ethics Committee Zone B, Milan, Italy; Ethics Committee of University of Brugmann, Brussels, Belgium; Ethics Committee of Greece; Ministry of Health and Rabin Medical Center Ethics Committee, Israel.

Statistical analyses

Interactions were tested to assess the evidence whether the aspirin effect on the incidence of preterm-PE differed between subgroups defined by maternal age (<30 and ≥30 years), body mass index (<25 and ≥25 kg/m^2), racial origin (Afro-Caribbean, Caucasian and other), method of conception (natural and assisted by ovulation induction drugs or *in vitro* fertilization), cigarette smoking (smoker and non-smoker), family history of PE (present and absent), obstetrical history (nulliparous, multiparous with previous pregnancy complicated by PE and multiparous without PE), history of chronic hypertension (present and absent). For the medical conditions systemic lupus erythematosus, antiphospholipid syndrome

and diabetes mellitus, there were too few preterm-PE events for logistic regression. The subgroup analyses for obstetrical history were pre-specified but those for maternal characteristics and medical history were post hoc.

Interaction was tested by the addition of terms to the logistic regression model that was used for the primary analysis.[1] The estimated risk of preterm-PE at screening and the participating centre were included as covariates. In these analyses, continuous variables were grouped as indicated above. The analysis of these was repeated respecting the continuous scale and there was no substantive difference in the results. Treatment effects (odds ratios aspirin/placebo) were estimated by parameterizing the logistic regression model so that it included coefficients corresponding to within group log odds ratios. This is more efficient than separate analyses of different subgroups. Interaction tests were performed on the full data set of patients in the intention to treat population and on the data set comprising those patients who took $\geq$ 90% of the prescribed medication. Results are presented as a forest plot with P values for the interaction effects, group sizes, event counts and estimated odds ratios (aspirin/ placebo). We examined whether the test of interaction was significant at the 5% level; since the number of planned tests was 8 the P values should be compared to 0.05/8 = 0.00625 to determine significance at the 5% level with a Bonferroni adjustment for multiple comparisons.

Having identified those with chronic hypertension as a credible subgroup who may not benefit from taking aspirin, estimates of the effects of treatment according to history of chronic hypertension (present and absent) and adherence ≥90%were

obtained from the logistic regression model used for the primary analysis.[1] The statistical software package R was used for data analyses.[7]

Results

In the ASPRE trial preterm-PE occurred in 13 of 798 participants (1.6%) in the aspirin group, as compared with 35 of 822 (4.3%) in the placebo group (adjusted odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74; P = 0.004).[1]

There was no evidence of heterogeneity in the aspirin effect in subgroups defined according to racial origin, maternal age, body mass index, method of conception, smoking, family history of PE, obstetrical history, and history of pre-existing medical conditions, except for chronic hypertension in which there may not be a beneficial effect from aspirin (Figure 1). The subgroup of medical conditions other than chronic hypertension is not shown in the figure because there were no cases of preterm-PE in the 19 participants of the aspirin group and only 1 in the 8 of the placebo group (odds ratio 0.00, 95 CI 0.00 to infinity).

In participants with chronic hypertension, preterm-PE occurred in 10.2% (5/49) in the aspirin group and in 8.2% (5/61) in the placebo group (odds ratio 1.29, 95% confidence interval, 0.33 to 5.12); the respective values in those without chronic hypertension were 1.1% (8/749) in the aspirin group and 3.9% (30/761) in the placebo group (odds ratio 0.27, 95% confidence interval, 0.12 to 0.60) (Figure 2). In all participants with adherence of $\geq$90% the adjusted odds ratio in the aspirin group was 0.24 (95% CI 0.09 to 0.65), in the subgroup with chronic

hypertension it was 2.06 (95% CI 0.40 to 10.71) and in those without chronic hypertension it was 0.05 (95% CI 0.01 to 0.41). For the complete data set the test of interaction was not significant (p=0.055 without and 0.44 with Bonferroni correction), but in those with adherence ≥90% the interaction was significant (p=0.0019 without and 0.015 with Bonferroni correction).

Comment

Principal findings of this study

The ASPRE trial demonstrated that, in women with singleton pregnancies identified by means of first trimester screening as being at high risk for preterm-PE, the administration of aspirin at a dose of 150 mg/day from 11 to 14 weeks until 36 weeks' gestation reduces the incidence of preterm-PE by approximately 60%.[1] A secondary analysis demonstrated that the beneficial effect of aspirin depends on adherence and the reduction in incidence of preterm-PE may be about 75% in those with adherence of ≥90% and only 40% in those with adherence of <90%.[8]

This subgroup analysis demonstrated that there was no evidence of heterogeneity in the beneficial effect of aspirin in reducing the incidence of preterm-PE in subgroups defined according to maternal age, body mass index, racial origin, method of conception, smoking, family history of PE, obstetrical history, and history of pre-existing medical conditions, except for chronic hypertension. In chronic hypertension prophylactic use of aspirin may not be useful in the prevention of preterm-PE. Consequently, if participants with chronic

hypertension were excluded from the trial, aspirin could have potentially reduced the incidence of preterm-PE by >70% and this reduction could have been about 95% in those with adherence of ≥90%. However, there is a high degree of uncertainty about these post hoc findings and further evidence is needed. We are planning a clinical evaluation study that will address this.

Limitations of the study

The ASPRE trial had demonstrated the therapeutic efficacy of aspirin globally and the size of the treatment effect was consistent across estimated risk groups for preterm-PE at the time of screening.[1] The estimated risk for preterm-PE was derived from an algorithm combining maternal factors with biomarkers[2] and there was considerable heterogeneity in maternal characteristics and medical and obstetrical history in the trial population. It is for this reason that we wanted to ascertain whether there are differences in the therapeutic efficacy in subgroups of the population defined according to maternal characteristics and medical and obstetrical history.

The ASPRE trial was powered for a global test of the aspirin effect in a high risk population. The statistical power for detecting effects in smaller subgroups of data is inevitably poor and only the larger interaction effects are likely to be detected. This problem is exacerbated by the need to account for multiple comparisons. It is reassuring that the estimated odds ratios for groups other than chronic hypertension show a degree of consistency. However, the confidence intervals are very wide and we cannot rule out clinically important interaction effects.

Clinical implications of the study

The argument in favour of first-trimester screening for PE has been strengthened by the findings of the ASPRE trial which demonstrated that in women identified by such screening as being at high-risk for preterm-PE administration of aspirin can reduce substantially the incidence of the disease.[1,9] The results may help resolve the controversy concerning the relation of the therapeutic effect of aspirin with the gestational age at onset of therapy and the necessary dose of the drug.[10-13]

The subgroup analysis demonstrated that in women with chronic hypertension aspirin may not be useful in the prevention of preterm-PE. The European Medicines Agency proposed that the credibility of a finding of inconsistency for the therapeutic effect in a subgroup, compared to the whole trial population, requires that tests of interaction are statistically significant, there is supportive evidence from other trials, and there is a biological plausibility for the findings.[14] We found that in the subgroup with chronic hypertension and adherence ≥90% the test of interaction was highly significant. Our results that aspirin may not be effective in women with chronic hypertension are concordant with those of a meta-analysis of individual patient data from 32 217 women recruited to 31 trials on the use of antiplatelet agents, mainly aspirin, for prevention of PE which reported a subgroup analysis according to pre-existing hypertension.[15] The relative risk (with 95% confidence interval) for all women was 0.90 (0.84 to 0.97), in the subgroup of women with pre-existing hypertension it was 0.97 (0.84 to 1.12) and in those without pre-existing hypertension it was 0.88 (0.81 to 0.96); however, the test of interaction was non-significant (p=0.28).

In terms of biological plausibility there is some evidence of differences between chronic hypertension and other factors in the pathogenesis of PE. Chronic hypertension, found in 1-2% of pregnancies, is the strongest risk factor for PE compared to other factors in maternal demographic characteristics and medical history.[3] In women with chronic hypertension the risk of both preterm and term PE is 5-6 times higher than in women without this medical disorder.[16] Preterm-PE is associated with impaired trophoblastic invasion of the maternal spiral arteries, reduced placental perfusion, oxidative stress that triggers off release of trophoblast-derived factors which cause generalized endothelial dysfunction and an exaggerated inflammatory response that underlines many of the changes observed in PE.[17-21] In chronic hypertension there is endothelial dysfunction and inflammation even before pregnancy and it is possible that in this condition PE can develop in the absence or less severe degree of impaired placentation because the pre-existing endothelial dysfunction is exacerbated by the physiological burden of pregnancy.[22-27]

Conclusions

In pregnancies at high risk of preterm-PE identified by screening at 11-13 weeks' gestation administration of aspirin reduces the incidence of preterm-PE by about 60%.[1] Post-hoc analysis suggests that the reduction in preterm-PE may be 75% if adherence to medication is $\geq$90%[8] and could be as high as 95% if women with chronic hypertension are excluded. These analyses also suggest that in women with chronic hypertension aspirin may not reduce the incidence of preterm-PE.

Figure legends

Figure 1. Odds ratio for preterm preeclampsia in the aspirin group with 95% confidence intervals in different subgroups defined according to maternal characteristics and medical and obstetrical history. The P values and confidence intervals are not adjusted for multiple comparisons. We performed 8 tests and the P values should be compared to 0.05/8 = 0.00625 to determine significance at the 5% level with a Bonferroni adjustment for multiple comparisons.

Figure 2. Odds ratio for preterm preeclampsia in the aspirin group with 95% confidence intervals in the total population and in those with and without chronic hypertension and in subgroups with adherence of $\geq$90%.

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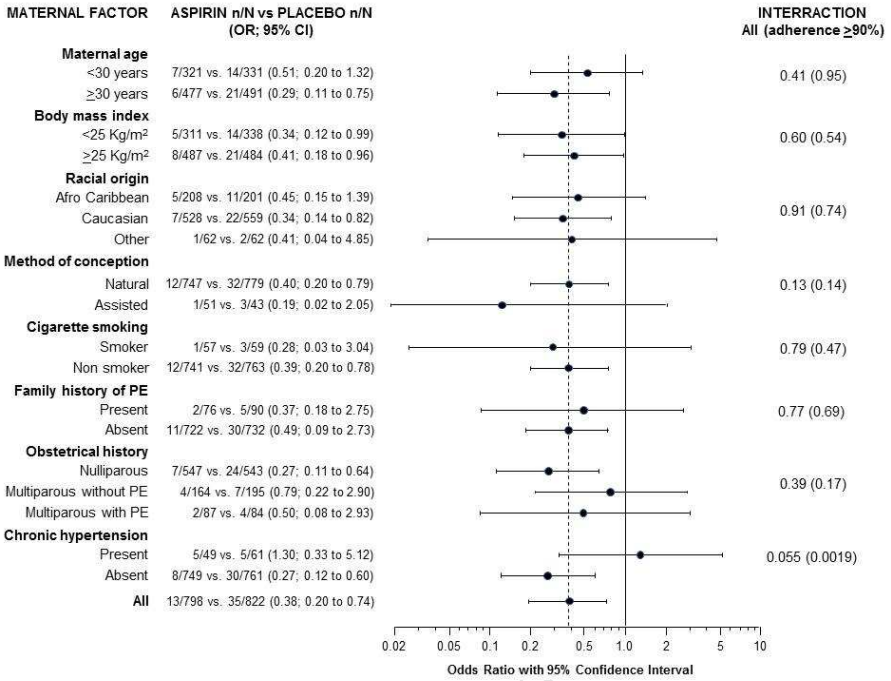

Figure 1

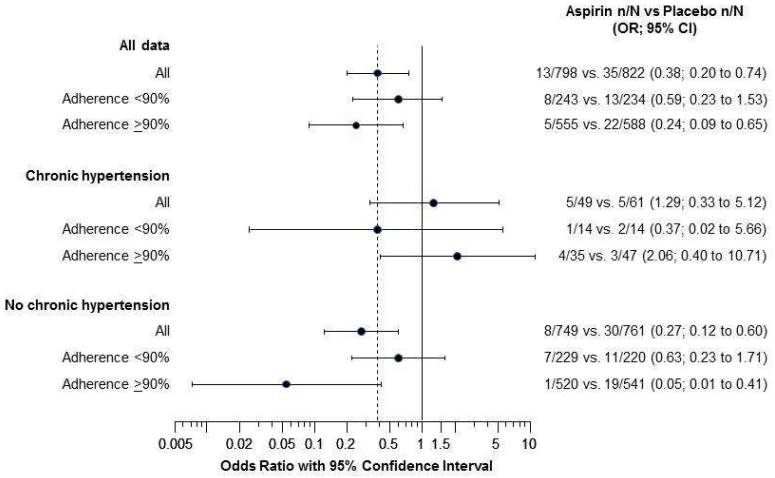

Figure 2